Prediction of omeprazole's disposition and drug-drug interactions using a physiologically-based pharmacokinetic model

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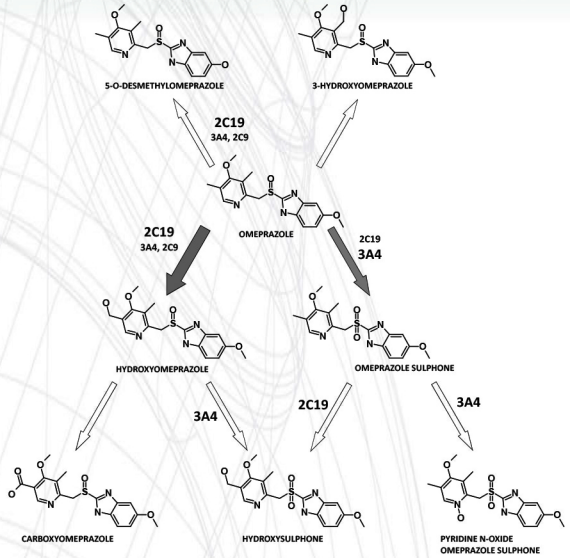
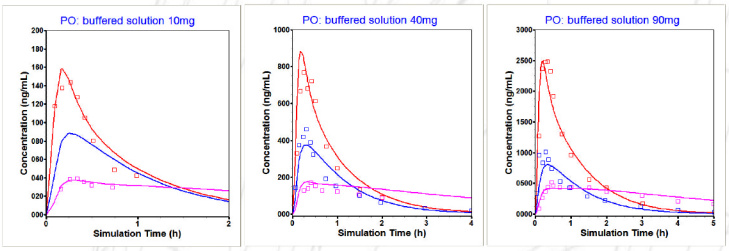
Abstract:

A detailed model describing the absorption and pharmacokinetics of omeprazole and its main metabolites, hydroxyomeprazole and omeprazole sulphone, was built using GastroPlus™ (Simulations Plus, Inc.). The program's Advanced Compartmental and Transit (ACAT) model described the absorption; the pharmacokinetics of all compounds was simulated with a physiologically-based pharmacokinetics (PBPK) model. The metabolic clearance of omeprazole and its metabolites in gut and liver was estimated from *in vitro* enzyme kinetic constants for CYP3A4, 2C9 and 2C19 combined with built-in *in vitro* values for the distribution of 3A4 in gut and the average expressions of all three enzymes in liver or fitted to observed *in vivo* plasma concentration-time (Cp-time) profiles. The model accurately described pharmacokinetics of each compound after different intravenous (IV) and oral (PO) doses of omeprazole in different populations of subjects. The model was then used to predict the effect of fluvoxamine on the pharmacokinetics of omeprazole in extensive and poor metabolizers, accounting for varying contributions of the fluvoxamine-omeprazole and omeprazole-metabolite drug-drug interactions in each group of subjects.

Omeprazole's metabolic profile:



Dose-dependency of omeprazole's pharmacokinetics:

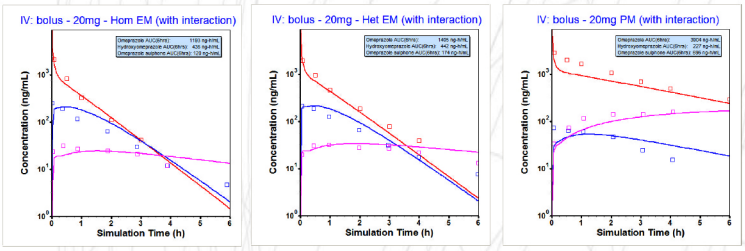


Pharmacokinetics of omeprazole (red) and its two main metabolites, hydroxyomeprazole (blue) and omeprazole sulphone (magenta), after increasing doses of buffered PO solution of omeprazole in Western subjects. The subjects in this study were not genotyped and a general population of extensive metabolizers with respect to CYP 2C19 was assumed. Simulated Cp-time profiles (solid lines) showed good agreement with reported [3] *in vivo* profiles (points) for all doses and compounds. A single absorption/pharmacokinetic model was used in simulations for all three doses.

Omeprazole is mainly metabolized by CYPs 2C19 and 3A4 [1,2]. The contribution of these two enzymes to the overall clearance of omeprazole varies in the range of about 70-97% for 2C19 and 2-20% for 3A4 depending on the CYP 2C19 genotype. A small contribution of CYP 2C9 toward the formation of one of the minor metabolites, 5-O-demsethylomeprazole, was observed *in vitro* [2]. The current model incorporates explicit contributions of 2C19, 3A4 and 2C9 to the formation of hydroxyomeprazole and omeprazole sulphone and to their subsequent metabolism. The remaining pathways of the metabolic profile were included as a non-specific clearance.

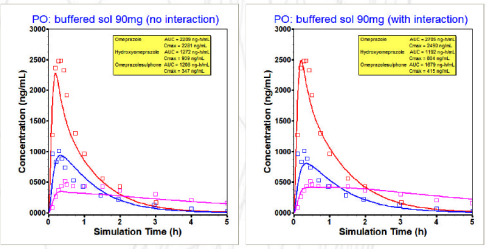
Effect of dosing route on omeprazole-metabolite DDI:

Since omeprazole's metabolites are eliminated by the same enzymes as omeprazole, it is expected that omeprazole and its metabolites will act as competitive inhibitors of each other *in vivo*. Simulations exploring this effect were performed with IV as well as PO dosing. All simulations utilized the baseline model as optimized against different PO doses and adjusted for individual populations: different expression levels of CYP enzymes in Japanese vs. Western population and different 2C19 Km values for extensive and poor metabolizers. Heterozygous extensive metabolizers (Het EM) were simulated well with the Km values from the baseline model. For homozygous extensive metabolizers (Hom EM) all 2C19 Km values were decreased by 25% and for poor metabolizers (PM) all 2C19 Km values were increased 10-fold.



The plots on the left show results of simulations incorporating the competitive interactions in different groups of Japanese subjects after IV dosing of omeprazole. Irrespective of genotype, the interactions did not have a significant effect on the AUC of omeprazole or hydroxyomeprazole (both compounds showed 1-2% change in AUC within 6 hr). A slightly higher change in the AUC of omeprazole sulphone was observed, where the simulations with interaction showed up to 20% increase in this metabolite's AUC compared to simulations without interaction. The largest effect was observed for the group of homozygous extensive metabolizers (Hom EM). Only ~2% increase in sulphone's AUC was observed in the group of poor metabolizers (PM). (Red – omeprazole, blue – hydroxyomeprazole, magenta – omeprazole sulphone, solid lines – simulated Cp-time profiles, points – *in vivo* Cp-time profiles [4])

The plots on the right show the simulated effects of competitive interactions between omeprazole and its main metabolites after PO dosing in Western subjects. AUCs of omeprazole and omeprazole sulphone increased by about 20% and 40%, respectively, due to competition for CYP 2C19. The AUC of hydroxyomeprazole decreased by ~6%. (Red – omeprazole, blue – hydroxyomeprazole, magenta – omeprazole sulphone, solid lines – simulated Cp-time profiles, points – *in vivo* Cp-time profiles [3]). One of the possible explanations for the different magnitudes of these interactions after IV and PO dosing is the effect of gut metabolism. After PO dosing, a significant amount of the omeprazole sulphone metabolite may be formed by CYP 3A4 in gut before parent omeprazole is metabolized by CYP 2C19 in liver. The metabolite is then able to compete with omeprazole for CYP 2C19 binding sites immediately as both compounds reach liver. After IV dosing, omeprazole sulphone is only formed in liver, resulting in a shift between the time when the parent omeprazole is first metabolized by CYP 2C19 and the time when the omeprazole sulphone metabolite accumulates to a sufficient degree to affect omeprazole's metabolism. This hypothesis is under further investigation.



Effect of fluvoxamine on pharmacokinetics of omeprazole:

The effect of fluvoxamine on the PK of omeprazole and its metabolites was predicted through dynamic simulation of the coadminnistration of omeprazole and fluvoxamine using an omeprazole model validated against data from IV dosing in Japanese subjects (as shown above). 40 mg of omeprazole was administered PO on the 7th day of 25 mg PO BID dosing of fluvoxamine. As expected based on the IV data, the predicted interaction was the same for homozygous and heterozygous EMs; however, the observed DDI [5] was higher in homozygous EMs due to the lower AUC in this group of subjects after administration of omeprazole alone. This might be due to different subjects being used in each study and contributions of other physiological factors than just the CYP 2C19 genotype.

	Hom EM	Het EM	PM
observed AUC ratio for omeprazole	4.86	2.08	1.23
Predicted AUC ratios			
omeprazole	1.67	1.71	1.4
hydroxyomeprazole	0.92	0.92	0.88
omeprazole sulphone	1.47	1.43	1.22

Hom EM – homozygous extensive metabolizers; Het EM – heterozygous extensive metabolizers; PM – poor metabolizers

Conclusions:

A single model was able to account for the pharmacokinetics of omeprazole and its metabolites in different populations (after accounting for physiological differences between populations). This comprehensive mechanistic model was used to explore the effects of individual compounds within the metabolic pathway on each other's pharmacokinetics as well as the effect of another compound (fluvoxamine) on their pharmacokinetics. Differences in DDI potential after different routes of administration and in different populations were also evaluated. Further uses of the model would include estimation of DDI potential for different dosing regimens of omeprazole and a second compound (administered simultaneously or with a certain time shift, etc.) to help with specifying recommendations for dosing in clinic.

References:

Andersson T. Br J Clin Pharmac 1994, 37: 597-604
Abelo A. Drug Metab Dispos 2000, 28: 966-972
Andersson T. Eur J Clin Pharmacol 1990, 39: 195-19
Ishizawa Y. Clin Pharmacokinet 2005, 44: 1179-1189
Yasui-Furukori N. Br J Clin Pharmacol 2004, 57: 487-494